Summit on Development of Infectious Disease Therapeutics

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Summary Draft Report of the Antifungal Working Group

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The working group recommended targeted investment in: diagnostics to enable trials to proceed; basic research that blended genomics, pathogenesis and target discovery; and the development of a clinical infrastructure.

Background and Existing Resources There is a critical medical need for the development of antifungal agents. Since there are no fungal vaccines currently licensed the only clinical recourse is the use of therapeutics. Current antifungal treatments are hampered by not being rapidly fungicidal, having limited spectrum, toxicity concerns, and emerging resistance. From the domestic perspective, fungal disease is a significant threat to patients receiving technically advanced and expensive treatments, such as immunocompromised patients seen in the transplant and cancer chemotherapy settings. Therefore, the mortality directly attributable to fungal infections carries exceedingly high attributable costs (e.g. loss of the organ transplant and the patient). From a global perspective, cryptococcosis is the second or third most common opportunistic infection in HIV/AIDS. In addition to previously mentioned limitations of current antifungal agents, formulations with reduced toxicity are so expensive that even domestic use must be carefully justified. This limits the availability of these drugs in developing countries. The role of fungi in chronic human illness is not known.

Currently, antifungal research is under-resourced. While there is a large and expanding population of patients infected with the medically important fungi, there are a relatively small number of patients that can be studied in a given trial, given the stringent eligibility criteria for entry, the confounding medical variables, and the lack of satisfactory diagnostics to identify the infected patients early enough to be viable candidates. Because of these challenges, well characterized specimen panels, which would aid in the development of improved diagnostic assays, are essentially unavailable. All of this has led to the false assumption that the actual number of patients infected is small. Genome sequencing is nearly finished for *Candida albicans*, on-going for *Cryptococcus neoformans*, and just beginning for 40% of the *Aspergillus fumigatus* genome. These scientific resources hold great potential to address the clinical need, especially in the neglected area of definitive diagnostic procedures or targets to identify infected patients and track their course of infection.

While large pharmaceutical companies are able to work within the time frames of the NIAID grant and contract mechanisms, rapid turnaround from submission to award is

important for smaller pharmaceutical companies. Furthermore large pharma owns chemical libraries which may be underutilized while small pharma can rapidly identify targets for antifungals but needs access to compounds to test against these targets. Academia develops promising targets and drug candidates but has difficulty moving these to clinical trials. Within NIAID, support opportunity for drug development and discovery is provided through unsolicited grant mechanisms, Small Business Innovative Research, research program projects, cooperative agreements, and contracts like that supporting the Mycoses Study Group.

New Opportunities for Drug Development for Fungal Diseases

The billion dollar sales of Fluconazole have validated the market for antifungal drugs, principally for the medically important yeasts. Yet, at present, there is not a single rapidly fungicidal, non-toxic drug available. Treatment priorities identified by the working group included drugs for aspergillosis and candidiasis. These drugs need to be fungicidal, broad spectrum, non-toxic, orally deliverable and low in cost. Comparative genomics may help to identify targets that are selective for the pathogen and thus, less toxic to the host. This is especially important since fungi are eukaryotic and have molecular similarities to their human host.

Diagnosis is the rate-limiting step preventing the advance of drug development for aspergillosis, and is a significant factor limiting advances in treatment of candidiasis. There is a clear role for government in addressing a means of establishing a direct (or surrogate) indication of early infection with Aspergillus fumigatus or A. flavus to validate the market for this infection for which: a) no current, effective therapeutic agent exits; b) even sub-standard but toxic therapy can be instituted at an early juncture; c) the patient population cannot be identified for enrollment in a prospective trial; and d) there is no reliable means by which to monitor response to treatment with the existing or experimental therapeutics. Life or death as an outcome is too crude an indicator to be practical, but all too often is the reality. Mortality exceeds 80% in a significant high risk group using available chemotherapy. Market size is estimated on the basis of proven infections, and there is no effective means for proving the infections. Risk group size and extrapolation from single center incidence data has not been a means of advancing pharmaceutical efforts to adopt the target of aspergillosis. The discovery of an agent highly active against aspergilli in vivo could validate the market for this expanding disease group in the same way that fluconazole validated the market for yeasts.

The working group also noted a number of unique aspects for the development of antifungal drugs. Fungi are associated with complex disease entities in complex medical patients, e.g. cryptococcosis in AIDS patients, or aspergillosis in bone marrow or organ transplant patients. Not only is the patient's immune status impaired but they are often receiving other antimicrobial prophylaxsis or therapy, have indwelling devices potentially seeding infectious agents, and have a disrupted normal flora that includes colonizing fungi with the ability to cause invasive disease as the host environment changes. Distinguishing between colonization and invasion in these hosts is critical. Protocols need to be designed to address both disease and patient complexities.

Moving Forward
While numerous impediments to drug discovery and development were identified, the following provides the suggestions of approaches to overcome these challenges.

The availability of characterized specimens for development and validation of diagnostic tests will facilitate research. Trained researchers are needed for both basic and clinical studies. There is a need for sharing gene chips, reagents and software. Epidemiological and pathogenicity studies are needed to develop information for clinical studies. Animal models for opportunistic infections need to be improved as do in vitro susceptibility tests.

Challenge grants were seen as one promising way to encourage research in these difficult areas.

Incentives
Pharma felt that patent extensions for even six months would encourage their support in developing drugs not expected to yield financial return. All agreed that the challenge grant format was useful as long as decisions and funding occurred in a short time. Support for creation of well characterized sample libraries during clinical trials could be leveraged to encourage development and validation of diagnostic assays.

Scientific/Technical Hurdles
Validated animal models and in vitro susceptibility testing that correlates with in vivo activity are lacking. The amount of infrastructure required to support animal studies is becoming prohibitive. Suggestions were made that perhaps a NIAID sponsored animal facility could facilitate the development of these models and provide support for studies, thus consolidating the infrastructure.

Logistical/Administrative/Legal Impediments
While there is a high need for clinical research the clinical capacity for the necessary trials is disproportionate to clinical need. A proposal to improve the efficiency of enrolling subjects included the creation of centers for the study of immune compromised patients at risk for invasive mycoses. This center approach would provide access to critically ill patients as well as providing specialty expertise for designing complex protocols dealing with the complexity of both patient and diseases. It would also provide the infrastructure to assist in enrolling patients in a timely manner. The NIAID Mycoses Study Group is a good model to build upon as is the NCI model of focused centers and infrastructure. A partnership among NIAID, NCI and industry for the development of centers for immunocompromised patients should be considered. See also the discussion above in "Scientific/Technical Hurdles" regarding animal models.

Training Needs
The working group identified a paucity of investigators trained to perform research in antifungal development, in particular with an understanding of the processes by which industry approaches the task. Suggestions were made that recruiting efforts should be instituted to attract and retain new investigators in this arena. Part of this training should

involve a 'sabbatical' with an industrial 'partner,' much like cooperative arrangements in many universities.

Support of basic research
Basic scientific research addressing discovery of targets, especially those found in fungi but not humans, for both antifungal agents and for sensitive, specific and early diagnostic detection systems needs to be fostered. This would include the areas of cell biology, particularly cell cycle, physiology, and cell wall structure as well as comparative genomics, i.e. separating pathogen from the host. In addition, the pursuit of immune based approaches to vaccine development should yield exciting progress in alternatives or adjuncts to antifungal interventions. The NIAID Mycology Research Units, three program project grants addressing prevention, diagnosis, and therapy of target diseases, have experienced success in focusing on pathogenesis and virulence mechanisms and should be built upon.

Working Together
Opportunities for government, academia and industry to collaborate were developed to include the sharing of gene chips and reagents as well as software for array analysis. Further, while performing clinical trials, industry could collect panels of well characterized specimens which then could be shared, to aid test development and validation, with companies that develop diagnostic assays. The opportunity exists to partner academic researchers and small pharma who are rich with potential targets with large pharma to validate these targets through testing with their chemical libraries.

Summary and Key Issues

- Critical medical need
- CHALLENGE GRANTS HAVE MULTIPLE PROSPECTS
- Recommend targeted investment in:

    1. Diagnostics/Awareness especially for aspergillosis to enable therapeutic development
    2. Basic science blending genomics, pathogenesis, and target discovery
    3. Clinical infrastructure
    4. Development of better animal models for studying the complexity of fungal diseases caused by opportunistic organisms
    5. Development of *in vitro* susceptibility tests which better correlate with in vivo activity as seen in the host.